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PCT/EP05/003384

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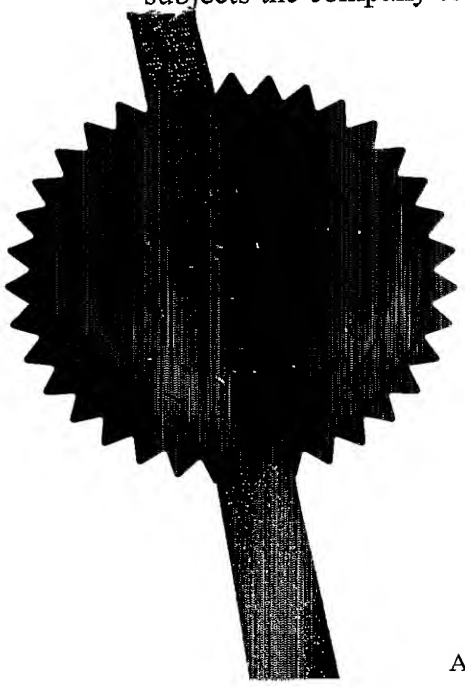

Signed William Mosell

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1. Your reference — 4-33700P2/NFI 8057

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2. Patent application number *(The Patent Office will fill in this part)* — 0407467.0

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

NOVARTIS AG
LICHTSTRASSE 35
4056 BASEL
SWITZERLAND

Patent ADP number *(if you know it)*

If the applicant is a corporate body, give the country/state of its incorporation — SWITZERLAND

7125487005

4. Title of invention — Organic Compounds

5. Name of your agent *(If you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Craig McLean
Novartis Pharmaceuticals UK Limited
Patents and Trademarks
Wimblehurst Road
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RH12 5AB

Patents ADP number *(if you know it)* — 07181522002

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Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing (day/month/year)

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Description	6
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Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
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11. I/We request the grant of a patent on the basis of this application

Signature Date

Craig McLean 1st April 2004

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Mrs S Schnerr 01403 323069

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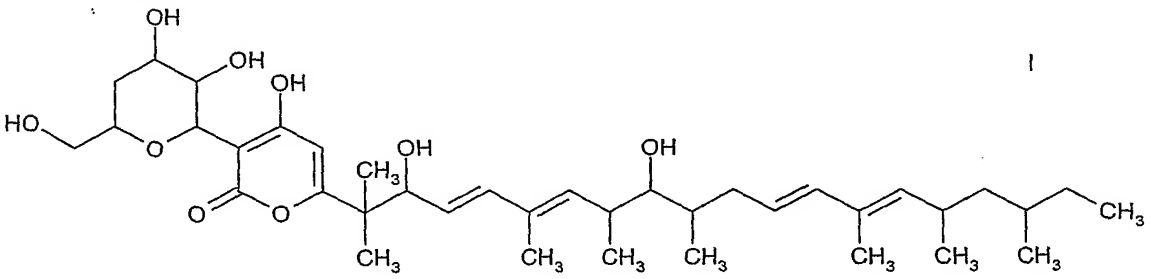
Organic Compounds

The present invention relates to organic compounds, such as the use of lactones as antiinflammatory agents.

In one aspect the present invention provides the use of a compound of formula



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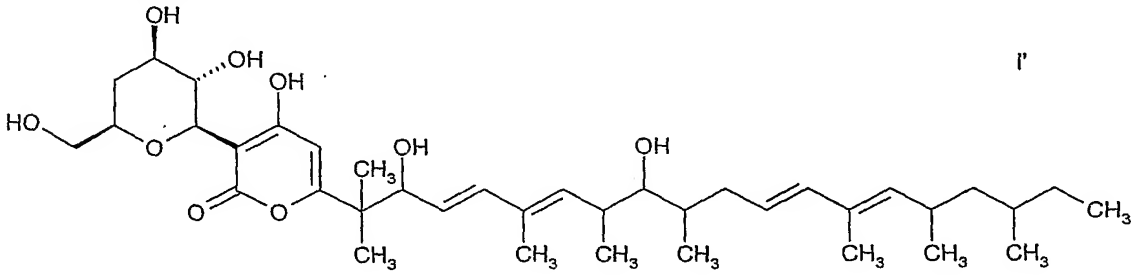
such as a compound of formula



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e.g. which is the compound acetic acid 7-acetoxy-1-[1-(3,4-diacetoxy-4'-hydroxy-6-hydroxymethyl-2'-oxo-3,4,5,6-tetrahydro-2.H.,2'.H.-[2,3']bipyranyl-6'-yl)-1-methyl-ethyl]-4,6,8,12,14,16-hexamethyl-octadeca-2,4,10,12-tetraenyl ester such as acetic acid (2E,4E,10E,12E)-7-acetoxy-1-[1-((2R,3R,4R,6R)-3,4-diacetoxy-4'-hydroxy-6-hydroxymethyl-2'-oxo-3,4,5,6-tetrahydro-2.H.,2'.H.-[2,3']bipyranyl-6'-yl)-1-methyl-ethyl]-4,6,8,12,14,16-hexamethyl-octadeca-2,4,10,12-tetraenyl ester,

for the preparation of a medicament for the treatment of diseases mediated by inflammation.

Treatment includes prophylaxis.

Compounds for use as provided by the present invention are hereinafter designated as "compound(s) of (according to) the present invention". A compound of formula I includes a compound of formula I'. A compound of the present invention includes a compound in any form, e.g. in free form, in the form of a salt, in the form of a solvate and in the form of a salt and a solvate.

Such salts include preferably pharmaceutically acceptable salts, although pharmaceutically unacceptable salts are included, e.g. for preparation / isolation / purification purposes.
A salt of a compound of the present invention includes a metal salt, e.g. or, where appropriate an acid addition salt. Metal salts include for example alkali or earth alkali salts, preferably alkali, such as lithium, potassium, sodium, preferably sodium.
A compound of the present invention in free form may be converted into a corresponding compound in the form of a salt; and vice versa. A compound of the present invention in free form or in the form of a salt and in the form of a solvate may be converted into a corresponding compound in free form or in the form of a salt in non-solvated form; and vice versa.
A compound of of the present invention may exist in the form of isomers and mixtures thereof; e.g. optical isomers, diastereoisomers, cis/trans conformers. A compound of the present invention may e.g. contain asymmetric carbon atoms and may thus exist in the form of enatiomers or diastereoisomers and mixtures thereof, e.g. racemates. Any substituent bound to an asymmetric carbon atom may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. For example, the tetrahydropyranyl ring and the nonadeca-alkenyl chain in a compound of formula I comprises asymmetric C-atoms and substitutents attached to such asymmetric C-atoms, such as hydroxy, methyl or the pyranyl ring, may be in the (R)- or in the (S)-configuration, e.g. as set out in a compound of formula I' or as set out in the chemical name of a compound of formula I'. Additionally a compound of formula I comprises double bonds in the nonadeca-alkenyl chain and substituents bound to such a double bond may be cis- or trans-confomers. Preferably the configuration of substituents attached to asymmetric C-atoms of a compound of formula I and the confomers in a compound of formula I are the same as in a compound of formula I, if the starting material for its production, namely a compound of formula II (as set out below) is obtained by fermentation (see production process below).
Isomeric mixtures may be separated as appropriate, e.g. according, e.g. analogously, to a method as conventional, to obtain pure isomers. The present invention includes a compound of the present invention in any isomeric form and in any isomeric mixture.
The present invention also includes tautomers of a compound of formula I, where tautomers can exist.

A compound of formula I, or of formula I', respectively, may be obtained as appropriate, e.g. according, e.g. analogously, to a process as conventional, e.g. e.g. by culturing a strain

producing a compound of formula III, e.g. a strain of the genus Microsphaeropsis Hohn, such as the fungus strain NRRL 15684, in the presence of a culture medium and recovering a compound of formula III from the culture medium, e.g. by chromatography, see e.g. US4753959.

The compounds of the present invention, e.g. including a compound of formula I and of formula I', exhibit pharmacological activity and are therefore useful as pharmaceuticals. In particular surprisingly the compounds of the present invention show anti-inflammatory activity and are e.g. useful in diseases associated with inflammation.

Antiinflammatory activity may be tested in test systems in vivo, namely in the IL-8 induced leucocytes emigration model, in the Topical ICD-TPA mouse model and in the ACD mouse model, e.g. as described below, wherein the following abbreviations are used:

ACD	allergic contact dermatitis
DAE	mixture of acetylacetamide, ethanol and acetone
ICD	isocitric dehydrogenase
PBS	phosphate buffered saline
TPA	12-O-tetradecanoyl phorbol-13-acetate (phorbol-12-myristate)

Test compounds include compounds of the present invention of formula I, namely of formula I'.

TEST SYSTEMS

1. IL-8 induced leucocytes emigration model

Comprise 24 to 36 female Balb/c mice, 18 - 20 g; IL-8 control group; reference group; buffer control group and 3 to 6 test groups. Human recombinant IL-8 is injected at 1 μg in 100 μl PBS i.p..

5 mg of a test compound, or reference compound, respectively, is dissolved in 1 ml of PBS. Immediately after i.p. injection of IL-8 100 μl of the test compound-solution are injected i.v. (= 500 μg/mouse). 4 hours after IL-8 injection the mice are anaesthetized and blood is collected by orbital puncture. The mice are sacrificed and peritoneal exudate cells harvested as follows: 5 ml of PBS are injected i.p. and after 1 minute as much of it as possible is recovered. Total cell counts of blood and peritoneal cells are performed on the Toa-Counter (Coulter).

The cytospin preparation is done on the Shandon Cytocentrifuge "Cytospin" 2. The blood smears and cytospin preparations are stained with Hemacolor (Merck). Differential cell counts of blood smears and peritoneal cells are performed under the microscope. Statistical evaluation (t-test) of the results is performed.

The compounds of the present invention show activity in the IL-8 induced leucocytes emigration model.

2. Topical ICD-TPA mouse model (TPA-induced irritant contact dermatitis)

10 µl of a 0.01% TPA solution is epicutaneously applied to the inner surface of the right ear of 8 NMRI mice per group for elicitation of an inflammatory pinnal swelling.The test animals are treated topically with 10 µl of a test compound (dissolved in DAE) 30 minutes before the application of TPA; control animals are treated similarly with the vehicle DAE alone.
Six hours after TPA-treatment the animals are sacrificed, both ear lobes cut off at the basis and weighed. Difference in auricular weights are taken as a measure of inflammatory swelling [right (treated, irritated) vs left (untreated, non irritated) ears, in %].
The compounds of the present invention show activity in the ICD-TPA model.

3. Topical ACD-model (oxazolone-sensitized mice)

10 µl of 2% oxazolone is epicutaneously applied to the inner surface of the right ear of 8 NMRI mice per group which mice are sensitized against oxazolone. After 30 minutes the test animals are treated topically with 10 µl of a test compound (dissolved in DAE). Twenty four hours later the animals are sacrificed. Inflammatory swelling is measured as set out under point "2. Topical ICD-TPA mouse model" above.
The compounds of the present invention show activity in the topical ACD model.

The compounds of the present invention show therapeutic activity and are thus useful in the treatment of diseases associated with inflammation, e.g. for use as antiinflammatory agents, e.g. for use in the treatment of inflammatory disorders, such as in suppression of neoplastic diseases, e.g. inflammatory skin diseases and autoimmune diseases, such as: psoriasis, atopical dermatitis, contact dermatitis and related eczematous dermatitises, seborrheic dermatitis, atopic dermatits, phototoxic and photoallergic dermatitis, Lichen planus, Pemphigus, bullous Pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous easinophilias, Lupus erythematosus, Alopecia areata and acne.

For pharmaceutical use a compound of the present invention includes one or more, preferably one, compounds of the present invention, e.g. a combination of two or more compounds of the present invention.

The compounds of Examples 1 and 2 are preferred compounds of the present invention. The compounds of the invention may be administered in similar manner to known standards for use in the treatment of diseases associated with inflammation.

In a further aspect the present invention provides a method of treatment of diseases which are associated with inflammation, which method comprises administering to a subject in need of such treatment an effective amount, e.g. an antiinflammatory effective amount of a compound of the present invention; e.g. in the form of a pharmaceutical composition.

Treatment includes treatment and prophylaxis.
For such treatment, the appropriate dosage will, of course, vary depending upon, for example, the chemical nature and the pharmakokinetic data of a compound of the present invention employed, the individual host, the mode of administration and the nature and severity of the conditions being treated. However, in general, for satisfactory results in larger mammals, for example humans, an indicated daily dosage is in the range from about 5 mg to about 1500 mg (ca. 0.06 mg/kg to ca. 20 mg/kg body weight), such as about 50 to about 1200 mg (ca. 4 mg/kg to ca. 15 mg/kg body weight) of a compound of the present invention; conveniently administered, for example, in divided doses up to four times a day.
A compound of the present invention may be administered by any conventional route, for example enterally, e.g. including nasal, buccal, rectal, oral, administration; parenterally, e.g. including intravenous, intramuscular, subcutanous administration; or topically; e.g. including epicutaneous, intranasal, intratracheal administration;
e.g. in form of coated or uncoated tablets, capsules, (injectable) solutions, solid solutions, suspensions, dispersions, solid dispersions; e.g. in the form of ampoules, vials, in the form of creams, gels, pastes, inhaler powder, foams, tinctures, lip sticks, drops, sprays, suppositories.
The compounds of the present invention may be administered in the form of a pharmaceutically acceptable salt, e.g. metal salt; or in free form; optionally in the form of a solvate. The compounds of the present invention in the form of a salt exhibit the same order

of activity as the compounds of the present invention in free form; optionally in the form of a solvate.

A compound of the present invention may be used for pharmaceutical treatment according to the present invention alone, or in combination with one or more other pharmaceutically active agents. Such other pharmaceutically active agents include e.g. other pharmaceutically active compounds which are active in the treatment of diseases associated with inflammation, e.g. and antibacterials.

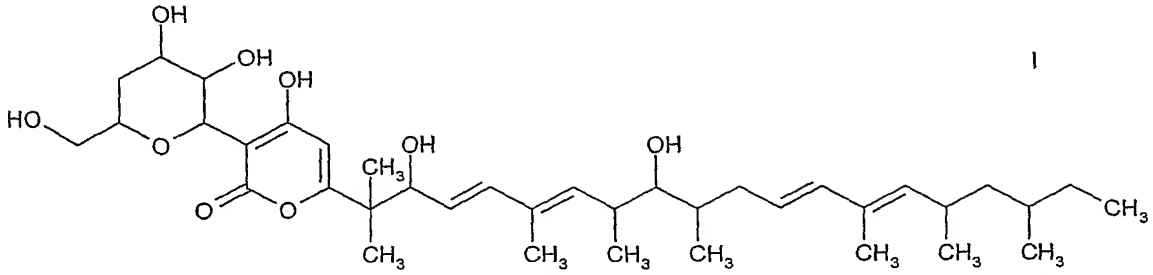
Combinations include fixed combinations, in which two or more pharmaceutically active agents are in the same formulation; kits, in which two or more pharmaceutically active agents in separate formulations are sold in the same package, e.g. with instruction for co-administration; and free combinations in which the pharmaceutically active agents are packaged separately, but instruction for simultaneous or sequential administration are given.

In another aspect the present invention provides a pharmaceutical composition comprising a compound of the present invention in association with at least one pharmaceutical excipient, e.g. appropriate carrier and/or diluent, e.g. including fillers, binders, disintegrators, flow conditioners, lubricants, sugars and sweeteners, fragrances, preservatives, stabilizers, wetting agents and/or emulsifiers, solubilizers, salts for regulating osmotic pressure and/or buffers, further comprising another pharmaceutically active agent.

Such compositions may be manufactured according, e.g. analogously to a method as conventional, e.g. by mixing, granulating, coating, dissolving or lyophilizing processes. Unit dosage forms may contain, for example, from about 50 mg to about 1000 mg, such as 100 mg to about 500 mg.

Patent Claims

1. Use of a compound of formula



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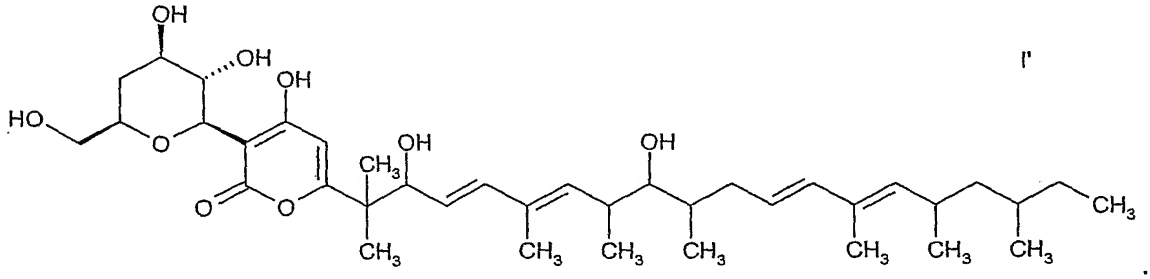
for the preparation of a medicament for the treatment of diseases associated with inflammation.

2. Use of claim 1, wherein a compound of formula I is of formula



I'

3. Use of any one of claims 1 or 2, wherein a compound of formula I is in the form of a salt.

4. Use of any one of claims 1 or 3, wherein a compound of formula I is in the form of an alkali salt.

5. Use of any one of claims 1 or 4, wherein a compound of formula I is in the form of sodium salt.

6. A pharmaceutical composition comprising a compound of any one of claims 1 to 5 beside at least one pharmaceutically acceptable excipient and further comprising another pharmaceutically active agent.

11. A method of treatment of diseases associated with inflammation which treatment comprises administering to a subject in need of such treatment an effective amount of a compound of any one of claims 1 to 5.

SC/3/26/2004

Abstract

Lactones, which are pharmaceutically active in diseases associated with inflammation.